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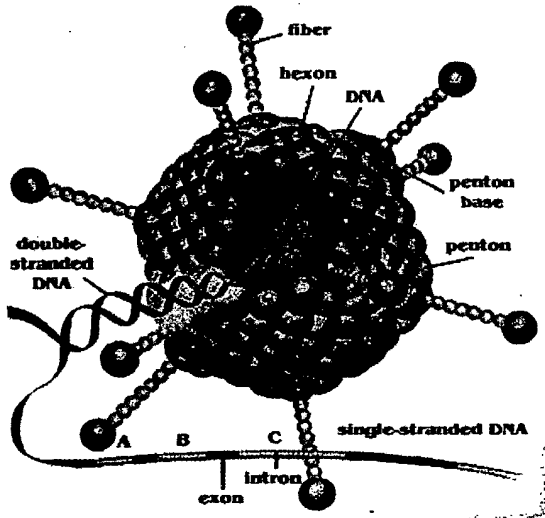
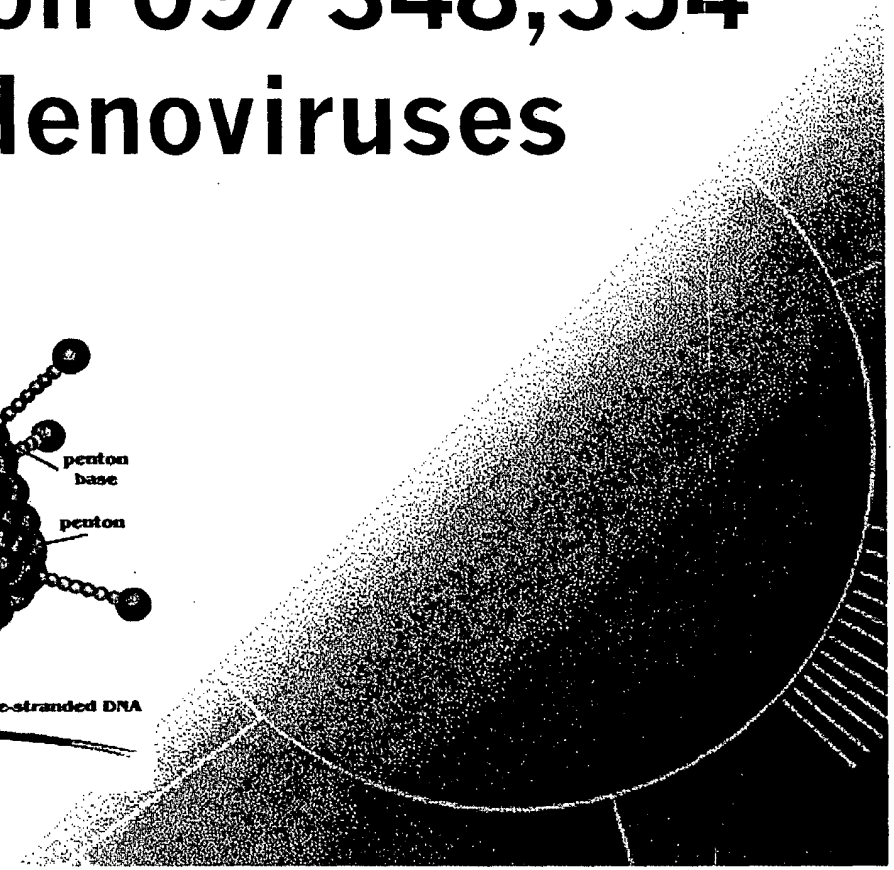
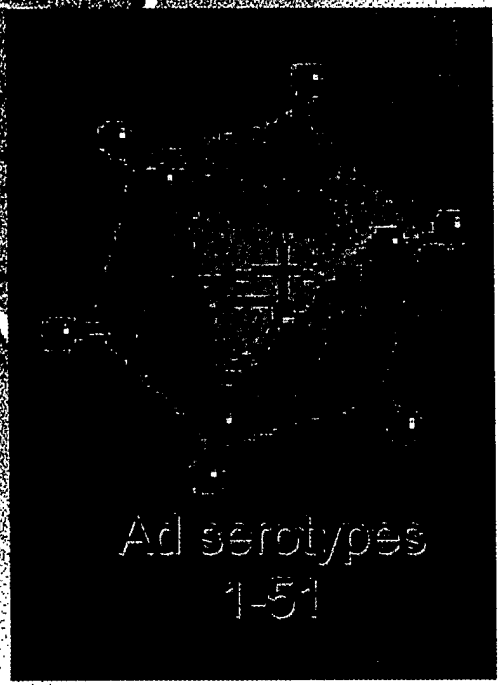
Patent application 09/348,354 "Chimeric adenoviruses



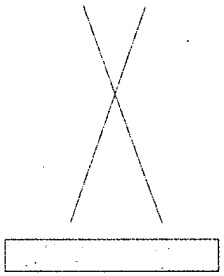


Capsid modified vector library

Adenovirus type 5



PCR amplify



Library of Fibers

7	16	33	45
8	17	34	47
9	24	35	49
10	27	37	50
11	28	38	
12	30	40-S	
13	32	40-L	

Production on PER.C6

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Definition of "Tropism"

Viral patent (US6,127,525):

"Receptor specificity or natural affinity for certain tissue of host organism".

Definition is limited to binding of virus to cell type due to compatibility of virus and cellular receptor.

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The sum of biological processes that determine whether a virus can transfer a gene in vivo to a particular cell, organ or tissue.

Anatomical barriers
Viral lysis by serum components (non-antibody related)
Neutralizing antibodies
Receptor-virus compatibility
Vector stability

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Example I: Anatomical barriers

1) Due to for instance vessel wall barrier the virus is unable to reach the target of interest.

2) Due to the size of Adenovirus, penetration in tumor tissue is severly limited.

3) Expression profile of Ad5 receptor does not correlate with observed Ad5 infection patterns in rodents

(Fechner *et al* Gene Ther. 1999 Sep;6(9):1520-35)

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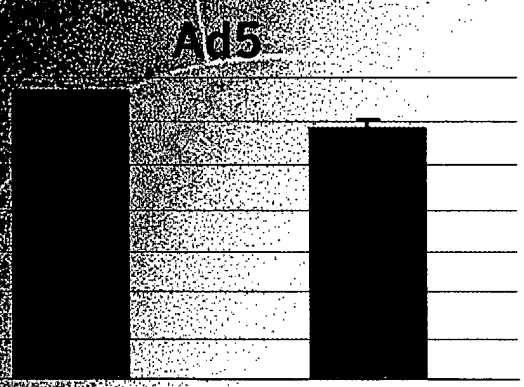
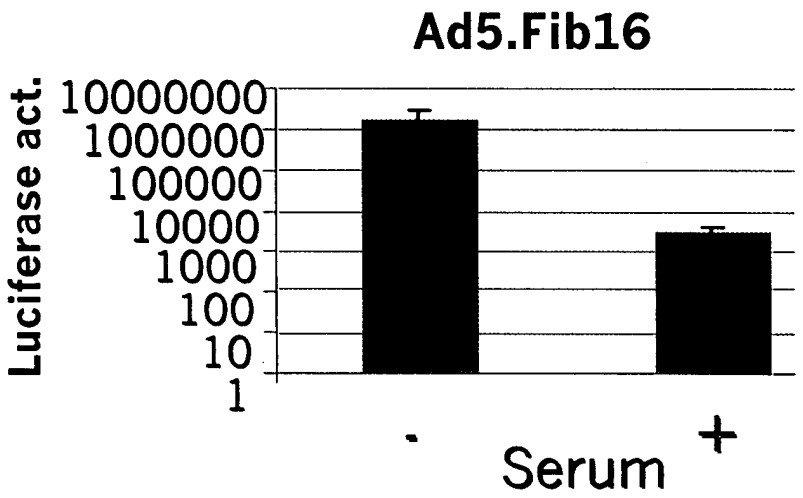
ample II: viral lysis by serum

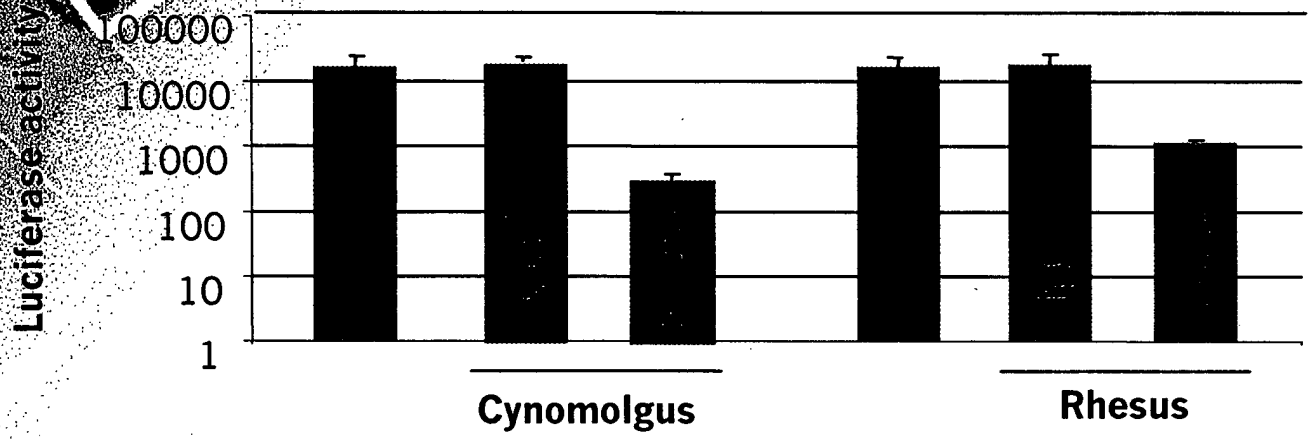
...key (pre-treatment)





¼ diluted serum, dose: 500 vp/ cell, A549 cells

Serum effect is independent of antibodies



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Postal patent (6,127,525): Concerning fiber swap and *in vivo* escape of Nab

Example 3 *(columns 25)*

"... These results confirm that switching the fiber from that of adenoviral serotype 5 subgroup C vector to that of an adenoviral serotype 7 subgroup B vector by itself is insufficient to allow the vector to escape neutralising antibodies generated against an adenoviral vector comprising Ad5 fiber....."

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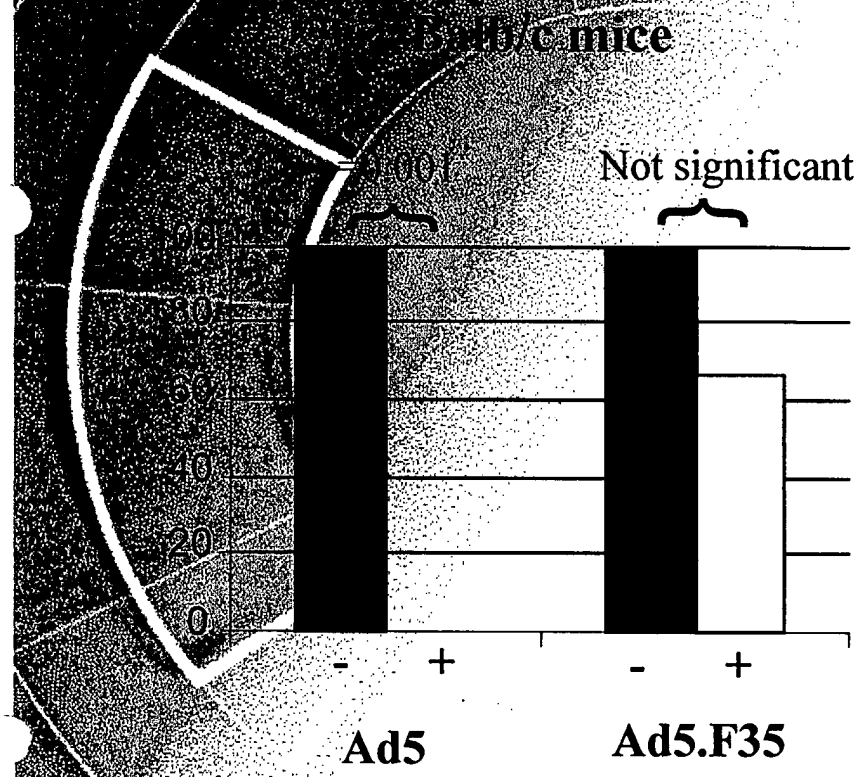
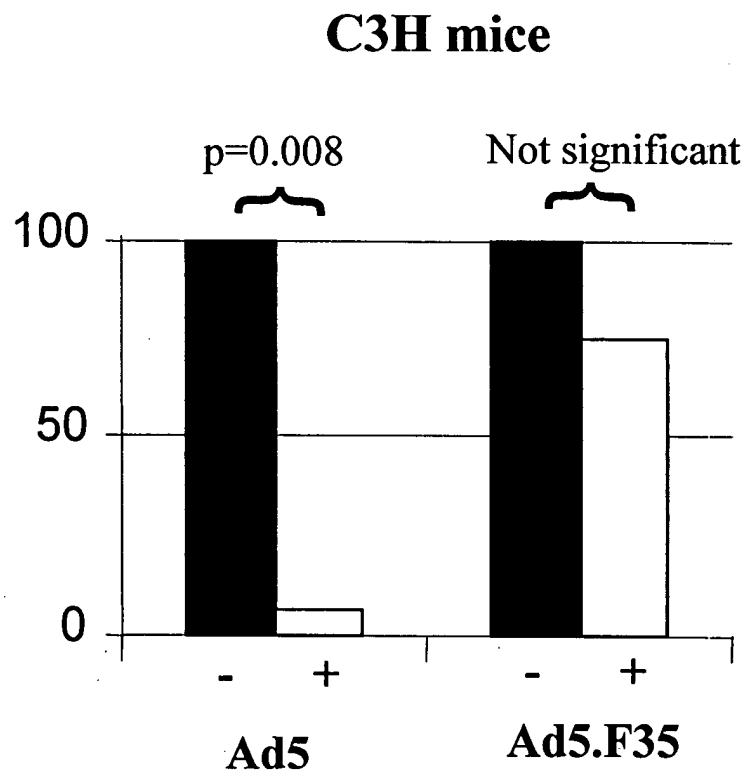
Slide III: Neutralizing antibodies





P values determined via "Mann-Whitney U" test

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Neutralizing antibodies

C57/ Bl6 mice

P values determined via "Mann Whitney U test"

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Differences in structural design of Fiber-chimeric vector

[illegible] patent:

- Complete deletion of Ad5 fiber and insertion of complete Ad7 fiber.

[illegible] et al. J.Virol Vol 70, p2120:

- "We have shown that amino acid homology between the tail regions of Ad5 and Ad7 is sufficient to allow functional replacement of the Ad5 fiber with Ad7 fiber."

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- Retained Fiber tail of Ad5 to ensure proper interaction with Ad5 penton-base (I.e. homology between Ad7 and Ad5 in fiber tail region is 57% on a.a. level)

Substantial difference in vector stability expected

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